Please amend the application as follows:

In the Claims

Claims 16 and 61 have been amended and are presented below in amended form. In accordance with 37 C.F.R. § 1.121(c)(1)(ii), amendments to the claims are indicated in the attached "Marked Up Version of Amendments" (page i).

16. (Three Times Amended) An isolated human CXC Chemokine Receptor 3 (CXCR3) protein or functional variant thereof, wherein said protein or variant can bind one or more chemokines and can mediate cellular signalling and/or a cellular response in response thereto, and wherein said protein or variant is encoded by a nucleic acid which hybridizes to a second nucleic acid selected from the group consisting of the complement of SEQ ID NO:1 and the complement of the open reading frame of SEQ ID NO:1 under high stringency wash conditions of 2X SSC, 0.1% SDS at room temperature for ten minutes followed by two washes in 1X SSC, 0.1% SDS at 65°C for thirty minutes and a final wash in 0.5X SSC, 0.1% SDS at 65°C for ten minutes.

61. (Twice Amended) A fusion protein comprising a human CXC Chemokine Receptor 3 (CXCR3) protein or functional variant thereof, wherein said CXCR3 protein or variant can bind one or more chemokines and can mediate cellular signalling and/or a cellular response in response thereto, and wherein said CXCR3 protein or variant is encoded by a nucleic acid which hybridizes to a second nucleic acid selected from the group consisting of the complement of SEQ ID NO:1 and the complement of the open reading frame of SEQ ID NO:1 under high stringency wash conditions of 2X SSC, 0.1% SDS at room temperature for ten minutes followed by two washes in 1X SSC, 0.1% SDS at 65°C for thirty minutes and a final wash in 0.5X SSC, 0.1% SDS at 65°C for ten minutes.

REMARKS

Claims 16 and 61 have been amended. Claims 16, 17, 19-21 and 60-84 are pending.

Claims 16 and 61 have been amended to recite high stringency wash conditions, and that the nucleic acid hybridizes "to a second nucleic acid selected from the group consisting of the complement of SEQ ID NO:1 and the complement of the open reading frame of SEQ ID NO:1

...." Support for the amendments is found, for example, at page 64, lines 6-12, and at the paragraph bridging pages 18 and 19.

The amended claims are supported by the specification as filed. Therefore, this amendment adds no new matter.

Additional remarks addressing the rejections set forth in the Office Action are set forth below under appropriate subheadings.

Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

Claims 16-17, 61-68 and 77-84 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a substantially purified polypeptide comprising an amino acid sequence as set forth in SEQ ID NO:2, is not deemed to reasonably provide enablement for amino acid sequences that are variants of said sequence or for a variant having at least 90% amino acid sequence identity to SEQ ID NO:2 (Claims 63, 64, 83 and 84). In maintaining the rejection, the Examiner again cites Mikayama *et al.* and Voet *et al.* (References U and V, of record) as evidence that it is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can alter the function of the protein. Based upon the teachings of these references, the Examiner concludes that the protein art is unpredictable and, therefore, that it would require undue experimentation for one of skill in the art to make and use the claimed invention.

It is well established that "[e]nablement is not precluded by the necessity for some experimentation such as routine screening." In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." Id. Accordingly, enablement does not require absolute predictability, but that the person of ordinary skill in the art be able to practice the invention without undue experimentation. Id.

The teaching Mikayama *et al.* and Voet *et al.* do not provide evidence that it would require undue experimentation to make and use the claimed invention, because enablement does

not require absolute predictability and because preparing and screening receptor proteins (or host cells that express recombinant receptor proteins) to identify those that have desired functions is routine in the art. This routine preparation and screening is analogous to the preparation and screening of hybridomas to identify those that produce a desired antibody, which the Wands court determined was not undue experimentation. In Wands, the court held:

> The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody. . . Furthermore, in the monoclonal antibody art it appears that an "experiment" is not simply the screening of a single hybridoma, but is rather the entire attempt to make a monoclonal antibody against a particular antigen. This process entails immunizing animals, fusing lymphocytes from the immunized animals with mycloma cells to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas for the desired characteristics.

Id. at 1406.

Like the monoclonal antibody technology considered by the Wands court, the nature of the instant technology area is that it involves preparing and screening proteins to identify those that possess desired characteristics. As was the case in Wands, upon consideration of the proper factors, no undue experimentation is involved.

The person of ordinary skill in the art would be able to practice the claimed invention following the guidance of the specification using no more than routine experimentation. As discussed in detail in Amendment A (Paper No. 7 at pages 5-8), methods suitable for preparing CXCR3 polypeptides that contain amino acid additions, deletions and/or substitutions were well known in the art at the time the application was filed. The Specification discloses and exemplifies methods for identifying CXCR3 proteins and functional variants that bind chemokine (e.g., IP-10, MIG) and mediate cellular signalling and/or a cellular response upon chemokine binding. Specification at page 39, line 1 *et seq.* and page 70, line 26 *et seq.*, for example. The Specification also teaches that CXCR3 is a G protein-coupled receptor and discloses the predicted domain structure of the protein. Id. at page 2, line 22 *et seq.*; page 8, line 22 *et seq.*; and Figure 2. Given this disclosure regarding CXCR3 together with the knowledge in the art of the structure-function relationship of G protein-coupled receptors, and the additional disclosure and exemplification provided, the person of ordinary skill in the art could practice the

claimed invention. In view of the teachings of the Specification and knowledge in the art, the person of skill in the art could readily prepare CXCR3 polypeptides, for example, those encoded by a nucleic acid that hybridizes to the complement of SEQ ID NO:1 under high stringency wash conditions and those sharing at least about 90% amino acid sequence identity with SEQ ID NO:2, using conventional techniques and could screen the proteins for chemokine (e.g., IP-10, MIG) binding and the capacity to mediate cellular signalling and/or a cellular response upon binding chemokine. Given the state of the art, the guidance in the specification, and detailed examples regarding how to assess functions of the polypeptides of the present invention, it would not require undue experimentation to make and use the invention as claimed.

Evidence of Enablement

Evidence that the specification contains an enabling disclosure and that the person of ordinary skill in the art would be able to practice the claimed invention using no more than routine experimentation is provided by subsequent publications by Lu *et al.* (Reference AX2, of record) and Soto *et al.* (Reference AY2, of record). Lu *et al.* and Soto *et al.* describe studies in which nucleic acids encoding a murine CXCR3 cDNA were isolated and cloned based upon hybridization using a cDNA probe corresponding to human CXCR3 or using degenerate primers and Polymerase Chain Reaction (PCR) technology, respectively. It is noted that Lu *et al.* were successful at isolating and cloning a nucleic acid encoding murine CXCR3 using methods that were well known in the art at the time the subject application was filed or are similar to the methods that Applicants describe in their specification (see, for example, Specification, at page 20, line 9 to page 21, line 20). Given the success that Lu *et al.* and Soto *et al.* had in isolating and cloning nucleic acids encoding murine CXCR3, it is apparent that given the teachings, exemplification and guidance provided by the subject application, the person of ordinary skill in the art would be able to practice the claimed invention without undue experimentation.

Evidence that the preparation of variant proteins containing amino acid substitutions and the screening of such proteins (or host cells that express such protein) to assess receptor-mediated functions are routine in the art is provided by Cunningham and Wells (Reference AW2, of record) and Holst *et al.*, "Steric Hindrance Mutagenesis Versus Alanine Scan in Mapping of Ligand Binding Sites in the Tachykinin NK_1 Receptor," *Molec. Pharmacol.* *53*:166-175 (1998) (copy provided as Exhibit A).

Cunningham and Wells describe a study in which 62 muteins of human growth hormone (hGH) containing single amino acid replacements were prepared and tested for binding to the human growth hormone receptor. Cunningham and Wells teach:

> Single alanine mutations (62 in total) were introduced at every residue contained within the three discontinuous segments of hGH (residue 2 to 19, 54 to 74, and 167 to 191) that have been implicated in receptor recognition.

Cunningham and Wells, Abstract, second sentence.

Thus, Cunningham and Wells specifically selected positions "that have been implicated in receptor recognition" for mutation. Notwithstanding the targeting of the amino acid substitutions to positions implicated in receptor binding, Cunningham and Wells report that "[t]he overall folding of these mutant proteins was indistinguishable from that of the wild-type hGH ...." Id. The results of the study demonstrated that although some mutants had lower affinity for receptor, many of the mutants displayed only minor changes in dissociation constant relative to wildtype (0.34 nM) and some bound with greater affinity. Cunningham and Wells at Table 1 (see, P2A (0.31 nM), T3A (0.31 nM), L9A (0.32 nM), R19A (0.37 nM), etc.). Thus, Cunningham and Wells demonstrate that at the time the subject application was filed, the person of ordinary skill in the art was well equipped to quickly prepare a large variety of mutants and to assess the mutants for desired function.

Holst *et al.* provide further evidence that the preparation and screening of variant or mutant proteins is routine in the art. Holst *et al.* describe a study in which muteins of the tachykinin NK_1 receptor, a 7-transmembrane G protein-coupled receptor, containing single or double amino acid replacements were prepared and screened for binding to non-peptide antagonists and to peptide antagonists. The muteins contained alanine substitutions or steric-hindrance mutations (i.e., substitutions with amino acids that have larger side chains than the naturally occurring amino acid) at positions implicated in ligand binding based upon structural similarity between the predicted tachykinin NK_1 receptor ligand binding site and the defined binding site for isoproterenol in the β2-adrenoceptor (β2-adrenergic receptor, another 7-transmembrane G protein-coupled receptor). Id. at 167, right column, lines 40-54. Some of the muteins produced and tested bound non-peptide antagonists with reduced affinity. Id. at page 172, right column, lines 11-17. However, Holst *et al.* teach that neither alanine substitutions nor steric hindrance mutations affected the binding affinity of peptide agonists on the NK_1 receptor,

and that "substance P [a peptide agonist] was able to stimulate phosphatidylinositol turnover in all these mutant receptors with a similar EC50 value as observed in the wild-type NK_1 receptor." Id. paragraph bridging pages 171 and 172; Fig. 4 and Table 4 (emphasis added). Thus, Holst *et al.* found that all mutant receptors tested bound the natural peptide agonist substance P and transduced signals in response to binding substance P.

Cunningham and Wells and Holst *et al.* demonstrate that the person of skill in the art was prepared to make and screen a large number of mutant or variant proteins, such as mutant or variant G protein-coupled receptors, in order to identify those that retained desired functions (e.g., binding and/or signalling). These references further demonstrate that even when amino acids in areas that are involved in binding function are substituted, variant proteins that retain binding function can be identified by routine screening. Cunningham and Wells and Holst *et al.* also demonstrate that although there is not absolute predictability in the protein art, the person of ordinary skill in the art at the time the application was filed, was able to make variant or mutant proteins that retained desired functions using no more than routine experimentation. Under the circumstances, the preparation of mutant or variant receptor proteins and screening same to identify those with desired functions cannot be considered undue experimentation.

In view of the foregoing, it is clear that the person of ordinary skill in the art would be able to practice the invention of Claims 16, 17, 61-68 and 77-84 using no more than routine experimentation. Reconsideration and withdrawal of the rejection are respectfully requested.

The Examiner additionally states that Claim 16 is rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Office Action at page 4, lines 3-9. The Examiner states that it is the sense strand of a double stranded nucleic acid that encodes the polypeptide and that the sense strand could not hybridize to itself.

In the interest of expediting prosecution, Claim 16 and Claim 61 have been amended to recite that the nucleic acid hybridizes to "a second nucleic acid selected from the group consisting of the complement of SEQ ID NO:1 and the complement of the open reading frame of SEQ ID NO:1," thereby obviating the rejection. It should be understood that Claims 16 and 61 encompass CXCR3 proteins or functional variants thereof that are encoded by single stranded nucleic acids or by double stranded nucleic acids.

Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph

Claims 16-17, 19-21 and 60-84 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner states that Claim 16 is indefinite in the recitation of the term "high stringency" and because it is unclear how a nucleic acid could hybridize to both a second nucleic acid and to a sequence complementary to the second nucleic acid.

Claim 16 and Claim 61 have been amended to recite high stringency wash conditions, and that the nucleic acid hybridizes to "a second nucleic acid selected from the group consisting of the complement of SEQ ID NO:1 and the complement of the open reading frame of SEQ ID NO:1," thereby obviating the rejection of these claims and claims dependent thereon.

Allowable Claims

Applicants thank the Examiner for indicating that Claims 19-21, 60 and 69-76 are allowable.

Attachment for PTO-948 and Request for Approval of Proposed Drawing Correction

The Office Action included an Attachment for PTO-948 (Rev. 03/01, or earlier). It appears that this attachment was included in error because form PTO-948 was not received with the Office Action and is not indicated as being attached on the Office Action Summary.

A Second Preliminary Amendment and Transmittal of Proposed Drawing Corrections and New Formal Drawings was filed in the USPTO on September 14, 2000. A copy of the post card date stamped by the USPTO and returned to Applicants' representatives acknowledging receipt of the Second Preliminary Amendment and Transmittal of Proposed Drawing Corrections and New Formal Drawings is provided herewith. Acknowledgment of acceptance of the proposed correction and of the new Formal Drawings is requested (e.g., in Office Action Summary Box 11) in the next Office Communication.